REMARKS

I. Status of the Claims

Claims 1-67 were originally filed. As a result of a restriction requirement, claims 19-44, 51-62, 65, and 67 were withdrawn from consideration. Subsequently, these withdrawn claims along with claims 11, 63, and 64 were canceled. Upon entry of the present amendment, claims 1-10, 12-18, 45-50, and 66 are pending under examination. In the June 4, 2003, Office Action, the Examiner has indicated that claims 45-50 are allowed, whereas claims 2, 4, 5, 10, 12, 13, 15, 17, and 66 are allowable but for their dependency from claim 1, which has been rejected for alleged anticipation.

Claim 7 is amended to replace "1-â-D-ribofuranosylimidazole-4-carboxamide" with "1-β-D-ribofuranosylimidazole-4-carboxamide," for the purpose of correcting a typographic error. Support for this amendment can be found in the specification on, *e.g.*, page 22, lines 28-29. Claim 18 is amended to adopt the form of an independent claim. No new matter is introduced by the present amendment.

II. Claim Objections

Claim 7 was objected to for containing a typographic error: the term "1-â-D-ribofuranosylimidazole-4-carboxamide" should be "1-β-D-ribofuranosylimidazole-4-carboxamide." The present amendment has corrected this error.

Claim 18 was also objected to as allegedly being improper dependent form for failing to further limit the claim scope. Upon entry of the present amendment, claim 18 has been rewritten to an independent claim. The objection for improper dependent form is thus obviated.

III. Claim Rejection

Claims 1, 3, 6-9, 14, and 16 were rejected under 35 U.S.C. §102(b) for alleged anticipation by Larsen *et al.* Applicants respectfully traverse the rejection.

To anticipate a pending claim, a prior art reference must provide, either expressly or inherently, each and every element of the claim. MPEP §2131. The present invention relates

to the novel strategy for inhibiting viral replication by using ribonucleoside analogs to increase the mutation rate of a virus, via a specific mechanism: the RNA nucleoside analog is incorporated by a polymerase into an RNA copy of a viral genomic nucleic acid, replaces a natural occurring nucleotide, and subsequently induces the virus to mutate by causing an incorrect nucleotide to be inserted in the position complementary to the analog incorporation site.

The Larsen *et al.* reference (co-authored by Mauchauffe, Hamelin, Peraudeau, and Tavitian) relates to inhibiting infectivity of Friend virus, a murine retrovirus, with Toyocamycin (TMC), an adenosine analog. Since TMC was observed incorporated in the viral RNA, the authors of the article speculated that "[t]he main consequence of such an incorporation ***should be*** a structural change in the secondary structure" and that "the Toyocamycin incorporation ***could possibly*** result in a miscoded message" (pages 1554 and 1555 of the Larsen *et al.* reference, emphasis added). Based on this speculation, the Examiner asserted that TMC causes increased viral RNA mutation by the claimed method, and therefore, the Larsen *et al.* reference anticipates pending claims 1, 3, 6-9, 14, and 16.

Applicants respectfully note that although Larsen *et al.* initially speculated the mechanism of TMC's action in inhibiting viral infectivity as by altering viral RNA structure and/or coding sequence, the same research group discovered in their later studies that TMC incorporation does not appear to lead to an altered reading frame. In a 1982 paper by the same group (Hamelin *et al.*, 1982, *Biochimie*, **64**:487-493, attached as Exhibit A), the authors (Hamelin, Madaule, Mathieu-Mahul, Honore, and Tavitian) concluded that TMC inhibits viral infectivity not by inducing mutations in viral RNA, but by some other mechanism yet to be fully illustrated. On page 493, left column, of the Hamelin *et al.* reference, the authors state:

> Toyomycin is incorporated into all RNA species studies so far in mammalian cells and one of the questions we asked was whether incorporation of the analogue in lieu of some adenosine residues in mRNAs would bring about some misreading frame. The answer seems to be no, as least for the viral messenger RNAs we, and others, studied. We had already shown that the replication of encephalomyocarditis virus was not affected by toyocamycin.

> Other authors also demonstrated that, in spite of the total inhibition of virus release, the viral mRNA and proteins of vesicular stomatitis virus were all present in the cytoplasm of toyocamycin-treated cells.

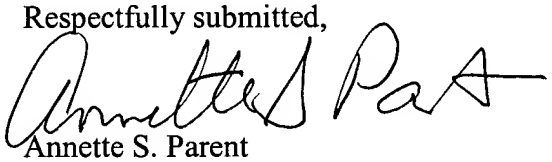
It is thus clear that the initial speculation of TMC causing viral RNA mutations, as offered by the Larsen *et al.* reference, has been recanted by the same research group in light of new evidence. As such, it has not been established that the Larsen *et al.* reference provides all elements of independent claim 1 (and thus its dependent claims) of the present application. Accordingly, Applicants respectfully request the withdrawal of the anticipation rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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Attachment (Exhibit A: Hamelin *et al.*, 1982, *Biochimie*, **64**:487-493)
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